JMSR
Journal of Medical and Surgical Research

Review

ISSN: 2351-8200

JMSR 2020 Vol. VI, n3: 714- 721

# COVID-19: A DIGESTIVE DISEASE!

Y. Cherradi,
Editor-in-Chief of Journal of Medical and Surgical Research
Department of Medicine, Mohammed V$^{th}$ Hospital, Sefrou, Morocco.

**ABSTRACT**

Since the first case of CoVID-19 pandemic has been reported in Wuhan in China, evidence of associated severe acute respiratory syndrome is well established and the disease is accepted as a primarily respiratory infection. However, current available data are supporting a gastrointestinal tropism with great implications at multiple levels in the course of this disease. The gastrointestinal tract appears in the heart of the strategy for management of infected patients from diagnosis to post-recovery isolation policies. This review highlights the digestive aspects of CoVID-19.

**Keywords:** ACE2, CoVID-19, Digestive, Endoscopy, Fecal transmission, Liver, Prognosis.

DOI: 10.46327/msrjg.1.000000000000159

DOI url: https://doi.org/10.46327/msrjg.1.000000000000159

**Corresponding Author:**
Dr Cherradi Younes**, MD.**
**Affiliation:** Department of Medicine, Mohammed Vth Hospital, Sefrou, Morocco.
**E-mail:** cherradiyounes@hotmail.com
**Tel.:** + (212)665659284



*****Published in May 02, 2020.*

## INTRODUCTION

The 2019–20 coronavirus pandemic is associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First identified in the city of Wuhan in Central China, CoVID-19 -which is the acronym of "coronavirus disease 2019"- was declared as a Public Health Emergency of International Concern In January, 30 2020 [1] and then characterized by World Health Organization as a pandemic on 11 March 2020. All ages are susceptible. Human to human contamination by the virus is well established by WHO [2]. CoVID-19 is primarily a respiratory infection with tropism to human airway epithelial cells [3] where the cellular receptor ACE2 is abundantly present [4, 5]. Mild or severe Pneumonia and acute severe respiratory illness are frequent respiratory complications [6]. The first commonly known agents of virus transmission are droplets generated by symptomatic patients in close contact when coughing, sneezing or talking [7, 8]. Are all of those elements mean that the gastroenterologists are not directly concerned by the CoVID-19 pandemic?

It's certainly not true, and many studies assessed the impact of coronavirus disease on the gastrointestinal system at multiple levels. Firstly, it has been shown that patients with CoVID-19 might present atypically gastrointestinal symptoms at the onset of the disease when respiratory complaints are still absent [9, 10]. Also, strong data support fecal–oral transmission of CoVID19 [8]; it is currently admitted as a potential route of virus spread. Third level is that some authors associate concurrent gastrointestinal (GI) symptoms to the severity of the disease [11]. Last point is the detection of presence of virus ARN present in feces samples even after an apparent recovery

JMSR
Journal of Medical and Surgical Research
Review
ISSN: 2351-8200
JMSR 2020 Vol. VI, n3: 714- 721

phase [12]. Considering all those findings, the gastrointestinal tract appears in the heart of the strategy for management of patients with CoVID-19 from diagnosis to isolation policies. CoVID-19 outbreak raises also issues related to protection of healthcare providers in endoscopy rooms and sterilization of endoscopy tubes. This review will focus on the aspects of the "digestive" CoVID-19 disease.

**Epidemiology and current status of the pandemic!**

Coronavirus disease 2019 (COVID-19), first reported in December 2019 in Wuhan in China, has reached a pandemic level. The causative agent is SARS-COV2, from the Coronaviridae family, is characterized by a high mutation potential and elevated mortality rate [13]. The number of CoVID-19 confirmed cases has reached more than 3.04 million cases in 185 countries as of April 27, 2020 leading to 211.000 deaths [14].

**GI symptoms in CoVID-19:**

While respiratory symptoms are typically major complaints in patients with CoVID-19, many patients reported gastrointestinal symptoms like diarrhea, vomiting and abdominal pain initially or during illness course [15- 17]. In first reports from Wuhan city, 2–10% of patients had gastrointestinal complaints [18- 20]. At the beginning of outbreak in Iran, doctors reported an unusual increase by 20% of the admissions in gastroenterology department; the patients reported diarrhea, vomiting abdominal pain and melena [10] and common therapeutic agents were unusually inefficient. They were all tested positive for SARS-CoV 2 [10].

GI symptoms are associated with coronaviruses and in outbreak of 2002–03, diarrhea was present in 16–73% of patients with SARS [21]. The mechanism of gastrointestinal tropism is explained by the affinity to ACE2 abundantly expressed in the glandular cells of gastric, duodenal, and rectal epithelia [22]. ACE2 - which is a membrane protein and inactivator of angiotensin II- is used by SARS-CoV2 as cell entry receptor [4]. The complex SARS-CoV2-ACE2 is endocytosed inducing release of pro-inflammatory cytokines and cellular damages. The invasion of enterocytes expressing ACE2 by SARS-CoV-2 causes malabsorption, unbalanced intestinal secretion leading to diarrhea [23]. Furthermore, the coronavirus 19 itself may be at the origin of disorders of the intestinal flora [25].

**Implications of digestive symptoms:**

In comparison with patients without CoViD-19 digestive symptoms, the presence of CoVID-19 GI manifestations was associated to longer discharge delay and laboratory evidence of prolonged coagulation and higher liver tests [23, 25]. It was also established that abdominal pain is significantly associated with increase of the disease severity and may be considered as a clinical predictive factor of severe forms [25]. In some studies, diarrhea was also mostly reported in patients with severe disease [11]; nausea, vomiting and diarrhea were significantly frequent in the group of patients who had acute respiratory distress syndrome and required mechanic ventilation [26]. This clinical association was not significant in other studies [19, 16].

**Detection of Viral ARN in feces and Evidence of fecal oral transmission of CoVID-19**

In the first US case of novel CoVID 19, the patient presented diarrhea at illness day 6 and stool samples collected a day later were tested positive by rRT-PCR [27] confirming the presence of the virus particles in feces and highlighting the possible fecal transmission. Presence of viral RNA in feces has been reported in many studies even during recovery period of CoviD-19 pneumonia [22, 28, 29]. It was suggested that survival period of viral particles was longer in gastrointestinal system than in respiratory [29]. Regarding those findings, it was important to assess about risk of fecal transmission in order to reduce the spread

JMSR
Journal of Medical and Surgical Research
ISSN: 2351-8200
Review
JMSR 2020 Vol. VI, n3: 714- 721

of disease and prevent contamination of patients' healthy family members and gastroenterologists when performing therapeutic or diagnosis endoscopies. Ong et al. established the risk of transmission in patient's environment by collecting samples from patient's bathroom and toilet area. Samples from the toilet bowl's surface, the sink (internal bowl) and the door handle detected the presence of SARS-CoV-2 while results were negative after cleaning [29, 30]. Toilets with poor sanitation may be a source of fecal oral transmission. Sharing toilets with CoVID-19 patients is not recommended even after discharge and recovery; they should be isolated in the following 14 days [29, 31]. It raises also the risk of contamination in asymptomatic patients and in pre-symptomatic period before respiratory symptoms are evident [29, 32, 33]. If there is no screening strategy, the failure to detect early this group of patients may contribute to continuous spread of the disease. For hospitalized patients, Xiao et al recommend PCR-test in feces routinely and maintain of transmission-based rules if results are still positive [22].

**Implications in endoscopy room:**

Gastroenterologists are required to establish clear algorithms and list of patients to reschedule. Unless in emergency cases (like acute gastrointestinal bleeding, acute cholangitis, foreign body retrieval...), endoscopy procedures should be postponed [34]. A list of prioritized procedures should be established. A screening of patients with risk of infection is recommended prior to endoscopy. Issues that should be investigated when patient is admitted are: recent travel to a high-risk area, medical history of recent fever, cough or dyspnea, or contact with an infected patient [23]. In Wuhan, screening CT scan was regularly performed before endoscopic procedures. Some centers opted for screening by IgM/IgG [35, 36]. The screening strategy model is certainly related to technical feasibility regarding accessibility and cost.

Considering the persistent fecal positivity by RT-PCR in recovering CoVID-19 patients, the timing of endoscopy is an issue. In this group of patients, except urgent cases, it seems preferable to perform that endoscopy at least 2 weeks after convalescence [35]. Some authors suggested stool testing as a risk stratification parameter [35].

If available, an isolated room with negative pressure should be dedicated to endoscopy [23, 35]. Wear of personal protective equipment (PPE) by gastroenterologists and nurses is mandatory. Staff members should be limited to minimal necessary for patient care and safety in order to minimize risk of healthcare exposure and optimize use of PPE. Other measures are recommended for patients with urgent indications for endoscopy including: reduce overcrowding and waiting times, wearing surgical masks and respect of hands hygiene rules and social distancing with at least 1 to 1.8 meters between patients in waiting rooms [35].

Like SARS CoV1, SARS CoV 2 is an enveloped virus inactivated by disinfectant agents with antiviral activity [23, 35, 37]. According to this, current protocols and existing guidelines seems efficient in reprocessing of scopes and endoscopic accessories [35, 38]. High level disinfection is indicated for scopes and sterilization for ''critical'' accessories [23, 39]. All surfaces in endoscopy room should be deeply cleaned daily with general disinfection.

Regarding biopsy specimen, the French Society of Digestive Endoscopy (SFED) recommended the use of formal in order to inactivate the virus in samples sent for histological study [40]. Tele-health is a good option for patients' follow-up; it's an opportunity to notify the development of recent CoVID-19 symptoms in the 14th days following endoscopic procedure and if yes, advise the staff who was possibly in contact with the infected patient [35].

**CoVID-19 and gut microbiome:**

The place of gut microbiome in the CoViD-19 digestive disease has been highlighted by some

ISSN: 2351-8200
JMSR 2020 Vol. VI, n3: 714- 721

authors. In some patients, a decrease in probiotics such as Lactobacillus and Bifidobacterium was reported suggesting an intestinal microbial dysbiosis [41]. Nutritional aspects are important in corrections of digestive disorders in CoVID-19. As a part of "Four-Anti and Two-Balance" strategy, medical staff in Zhejiang Hospital recommended use of prebiotics or probiotics for regulation of intestinal micro-ecological balance, correction of intestinal microbiota disorders and prevention of secondary infection induced by bacterial translocation [41].

Lactobacillus plantarum is largely used in food and medical industries as probiotic microorganism [42]. With its probiotic properties, the strong antiviral activity against coronavirus infection in porcine epithelial cell of the intestine was demonstrated. IFN-λ3 in Lactobacillus plantarum suppresses enteric coronavirus infection in epithelial cells of intestine of piglets which could be an option for oral therapeutic antiviral agent [43]. Prescription of probiotics may be with great support to the immune system against the virus. A preprint suggested the role of bacteria Prevotella in CoVID-19 pandemy, but there is no clear evidence regarding this.

**Liver manifestations in CoVID-19 disease:**

Many studies have reported liver impairment in CoVID19 patients suggesting that SARS-CoV2 may affect hepatocytes and hepatic functions [24, 45, 47]. Authors reported elevated levels of alanine aminotransferase and aspartate aminotransferase with prolonged coagulation in infected patients [24, 45] with increased incidence of abnormal liver function in severe forms of the disease [24, 46, 47]. A Chinese team from Shaanxi region concluded that critical illness was an independent risk factor for hepatic damage [46]. Liver injury might be explained by the abundant presence of ACE2 receptor in cholangiocytes [47] indicating a direct action on ACE2-positive hepatocytes responsible of hepatic dysfunction. Some authors suggested that mechanism of COVID-19 may be direct liver injuries due to a viral hepatitis [45], but post-mortem liver biopsies from infected patients showed microvesicular steatosis, -which is commonly found in case of sepsis [48]-, without viral inclusions in the liver [49]. Clinicians should pay special attention to patients with pre-existing liver disease. Because ACE2 gene is on the chromosome X, Pirola CJ et al. suggested clinical differences in the evolution of the disease in male patients with chronic liver disease compared to women [50]. Since ACE2 is expressed in low levels in the liver of women, severe liver injury may be prominent in men [50, 51].

## CONCLUSION

There is no doubt that CoVID-19 is primarily a respiratory infection with a spectrum of complication leading to death. But, in SARS CoV2, digestive symptoms may be inaugural and associated with longer discharge and severe presentations of the disease. Viral ARN is present in feces of asymptomatic patients and hepatic and intestinal viral tropism is established because of the abundance of ACE2 receptors. Oral fecal transmission is a potential route of continuous virus spread even after recovery of pneumonia. Regarding all those elements, CoVID-19 is also a digestive disease with highly implications on prevention and management strategy.

## ABBREVIATIONS:

SARS-CoV2: severe acute respiratory syndrome coronavirus 2.

ACE2: angiotensin-converting enzyme II.

GI: gastrointestinal.

CT: computed tomography.

IFN: interferon.

ISSN: 2351-8200
JMSR 2020 Vol. VI, n3: 714- 721

**DECLARATION OF INTERESTS:** None

**KEY POINTS:**

1- The gastrointestinal tract appears in the heart of the strategy for management of patients with CoVID-19 from diagnosis to isolation policies.
2- Digestive symptoms may be inaugural and associated with longer discharge and severe presentations of the disease.
3- Oral fecal transmission is a potential route of continuous virus spread even after recovery of CoVID-19 pneumonia.
4- Hepatic and intestinal viral tropism is the result of the presence of ACE2 receptors. ACE2 repartition may explain sexual dimorphism in CoVID-19.

**REFERENCES:**

1- Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)
2- Lake MA, What we know so far: COVID-19 current clinical knowledge and research. Clin Med (Lond). 20 (2), 124-127 (2020).
3- Wua YC et al. The outbreak of COVID-19: An overview. J Chin Med Assoc. 83 (3), 217-220 (2020).
4- Hirano T, Murakami M. COVID-19: A New Virus, but a Familiar Receptor and Cytokine Release Syndrome. Immunity. (2020) pii: S1074-7613(20)30161-8. doi: 10.1016/j.immuni.2020.04.003.
5- Sarzi-Puttini P et al. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol. 38(2):337-342 (2020)
6- Mungroo MR, Naveed Ahmed Khan A. and Siddiqui R. Novel Coronavirus: Current Understanding of Clinical Features, Diagnosis, Pathogenesis, and Treatment Options, Pathogens. 9(4): 297 (2020).
7- Singhal T. A Review of Coronavirus Disease-2019 (COVID-19) Indian J Pediatr. 87, 281–286 (2020).
8- Krajewska J. et al. COVID-19 in otolaryngologist practice: a review of current knowledge. Eur Arch Otorhinolaryngol (2020). https://doi.org/10.1007/s00405-020-05968-y
9- Lin L. et alGastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. (2020). doi: 10.1136/gutjnl-2020-321013
10- Hormati A et al., Can COVID-19 present unusual GI symptoms?, Journal of Microbiology, Immunology and Infection, (2020) https://doi.org/10.1016/j.jmii.2020.03.020
11- Jin X. et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut (2020). doi:10.1136/gutjnl-2020-320926
12- Ka Shing Cheung, Ivan FN. Hung, Pierre PY. Chan et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection andVirus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis. Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.03.065
13- Bajaj A, Purohit HJ. Understanding SARS-CoV-2: Genetic Diversity, Transmission and Cure in Human. Indian J Microbiol. 1-4 (2020). doi: 10.1007/s12088-020-00869-4.

ISSN: 2351-8200
JMSR 2020 Vol. VI, n3: 714- 721

14- 2019–20 coronavirus pandemic Wikipedia: https://en.wikipedia.org/wiki/2019%E2%80%9320_coronavirus_pandemic
15- Wong SH, Lui RN, Sung JJ. Covid-19 and the Digestive System. J Gastroenterol Hepatol. (2020). doi:10.1111/jgh.15047.
16- Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 382, 929-36 (2020).
17- Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 395, 514-23 (2020).
18- Zhou J. et al. Human intestinal tract serves as an alternative infection route for Middle East respiratory syndrome coronavirus. Sci Adv. 15; 3 (11) (2017). doi:10.1126/sciadv.aao4966
19- Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA (2020) doi:10.1001/jama.2020.1585
20- Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? Lancet Gastroenterol Hepatol. 5(4), 335-337 (2020).
21- WHO issues consensus document on the epidemiology of SARS. Wkly Epidemiol Rec. 78, 373–75 (2020)
22- Xiao F. et al. Evidence for Gastrointestinal Infection of SARS-CoV-2 Gastroenterology 1–3 (2020).
23- S. Musa, Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now? Arab Journal of Gastroenterology. 21 (20), 3- 8 (2020). https://doi.org/10.1016/j.ajg.2020.03.002
24- Lei Pan et al. Clinical Characteristics of COVID-19 Patients with Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. Am J Gastroenterol. 115, 766–773 (2020). https://doi.org/10.14309/ajg.0000000000000620
25- Henry BM., et al. Gastrointestinal symptoms associated with severity of coronavirus disease 2019 (COVID-19): a pooled analysis. Intern Emerg Med. (2020). doi: 10.1007/s11739-020-02329-9.
26- Guan W-J, Ni Z-Y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. (2020). doi: 10.1056/NEJMoa2002032.
27- Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis. (2020). pii: ciaa270. doi: 10.1093/cid/ciaa270.
28- Zhang T et al. Detectable SARS-CoV-2 Viral RNA in Feces of Three Children during Recovery Period of COVID-19 Pneumonia. J Med Virol. (2020). doi: 10.1002/jmv.25795.
29- Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther. 51 (9), 843-851 (2020).. doi: 10.1111/apt.15731.
30- Ong SWX et al. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. JAMA. (2020). doi: 10.1001/jama.2020.3227.
31- National Health Commission of the People's Republic of China. Guidance on coronavirus disease 2019 (COVID-19), China (Vision 7) (in Chinese). Published online March 3 (2020). http://www.gov.cn/zhengce/zhengceku/2020-03/04/content_5486705.htm

ISSN: 2351-8200
JMSR 2020 Vol. VI, n3: 714- 721

32- Bai Y. et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA. (2020 https://doi.org/10.1001/jama.2020.2565
33- Tong Z. et al. Potential presymptomatic transmission of SARS-CoV-2, Zhejiang Province, China, 2020. Emerging Infect Dis. 26(5), 1052-1054 (2020). https://doi.org/10.3201/eid2605.200198
34- Ponchon T., Chaudasse S. CoVID19: How to select patients for endoscopy and to reschedule the procedures. Endoscopy International Open. 8, 699-700 (2020).
35- Lui RN et al. Overview of guidance for endoscopy during the coronavirus disease 2019 pandemic. J Gastroenterol Hepatol. 2020. 35 (5):749-759. doi:10.1111/jgh.15053
36- Mao R. et al. Implications of COVID-19 for patients with pre-existing digestive diseases. Lancet Gastroenterol Hepatol. 5(5), 426-428 (2020).
37- Rabenau HF, Kampf G, Cinatl J, Doerr HW. Efficacy of various disinfectants against SARS coronavirus. J Hosp Infect. 61, 107–11 (2005).
38- Nelson DB, Muscarella LF. Current issues in endoscope reprocessing and infection control during gastrointestinal endoscopy. World J Gastroenterol. 12, 3953–64 (2006).
39- ASGE Quality Assurance in Endoscopy Committee, Calderwood AH, Day LW, Muthusamy VR, et al. ASGE guideline for infection control during GI endoscopy. Gastrointest Endosc. 87 (5), 1167–79 (2018).
40- Thesaurus national de cancérologie digestive version du 18/03/2020. www.tncd.org
41- Xu K. et al. Management of corona virus disease-19 (COVID-19): the Zhejiang experience. Zhejiang Da Xue Xue Bao Yi Xue Ban. 49 (1), 0 (2020).
42- Behera SS, Ray RC, Zdolec N. Lactobacillus plantarum with Functional Properties: An Approach to Increase Safety and Shelf-Life of Fermented Foods. Biomed Res Int. (2018) doi: 10.1155/2018/9361614.
43- Liu YS et al. Surface-displayed porcine IFN-λ3 in Lactobacillus plantarum inhibits porcine enteric coronavirus infection of porcine intestinal epithelial cells. J Microbiol Biotechnol. 30(4), 515-525 (2019). doi:10.4014/jmb.1909.09041.
44- Zhang C1, Shi L1, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 5(5):428-430 (2020). doi:10.1016/S2468-1253(20)30057-1.
45- Bangash MN1, Patel J2, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol. (2020). pii: S2468-1253(20)30084-4. doi:10.1016/S2468-1253(20)30084-4.
46- Yao N. et al. Clinical characteristics and influencing factors of patients with novel coronavirus pneumonia combined with liver injury in Shaanxi region. Zhonghua Gan Zang Bing Za Zhi.10, 28 (0), E003 (2020). doi:10.3760/cma.j.cn501113-20200226-00070.
47- Chai X. et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. bioRxiv (2020); published online Feb 4. https://doi.org/10.1101/2020.02.03.931766.
48- Koskinas J. et al. Liver histology in ICU patients dying from sepsis: a clinico-pathological study. World J Gastroenterol. 14, 1389–93 (2008).
49- Xu Z. et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet

ISSN: 2351-8200
JMSR 2020 Vol. VI, n3: 714- 721

Respir Med (2020) doi: 10.1016/S2213-2600(20)30076-X.
50- Pirola CJ, Sookoian S, COVID-19 and ACE2 in the liver and gastrointestinal tract: Putative biological explanations of sexual dimorphism. Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.04.050.
51- Tukiainen, T., Villani, A., Yen, A. et al. Landscape of X chromosome inactivation across human tissues. Nature 550, 244–248 (2017).